

The Application of Photodynamic Therapy in the Treatment of Periodontal and Peri-Implant Infections

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Running title: Photodynamic therapy in periodontal and peri-implant therapy

Abstract

Antimicrobial photodynamic therapy (PDT) has lately attracted much attention among clinicians for the treatment of pathogenic biofilm associated with periodontitis and peri-implantitis. However, at present, the data from randomized controlled clinical studies (RCTs) are still limited and, to some extent, controversial which makes it difficult to provide appropriate recommendations for the clinician.

Therefore, the aims of the present study were: a) to provide an overview on the current evidence from randomized controlled clinical studies evaluating the potential clinical benefit for the additional use of PDT to subgingival mechanical debridement (i.e. scaling and root planing (SRP)) alone in nonsurgical periodontal therapy and b) to provide clinical recommendations for the use of PDT in periodontal practice.

Based on the available evidence from RCTs the following conclusions can be drawn:

- In patients with chronic periodontitis (ChP) the combination of SRP and PDT may result in substantially higher short-term clinical improvements evidenced by probing depth (PD) and/or bleeding on probing (BOP) reductions compared to SRP alone.
- In patients with aggressive periodontitis (AgP) the use of PDT cannot replace the systemic administration of amoxicillin and metronidazole. Due to lack of data, no conclusions can be made to what extent PDT may replace the use of systemic antibiotics in patients with ChP.
- Limited evidence from one study indicates that PDT may represent a possible alternative to local antibiotics in patients with incipient peri-implantitis.

Key Words: Photodynamic therapy, chronic periodontitis, aggressive periodontitis, peri-implantitis, antibiotics, bacterial biofilm

Biological rationale

Periodontitis is a multifactorial disease which is associated with loss of the supporting tissues (i.e. periodontal ligament and alveolar bone) around the tooth.¹ A major objective of periodontal therapy is to remove soft and hard, supra- and subgingival deposits from the root surface in order to stop disease progression.² Numerous studies have reported significant improvements of clinical and microbial parameters following nonsurgical periodontal therapy.³⁻⁶

Despite the fact that non-surgical periodontal treatment may result in significant clinical improvements in the great majority of cases, evidence indicates that none of the currently available instrumentation techniques are effective in completely eliminating subgingival bacterial biofilm.⁷ These limitations may be attributed to several factors such as the complex anatomy of teeth (i.e. furcation involvements, root invaginations), presence of intrabony defects, etc., mechanical limitations related to the size of instruments or invasion of periodontal pathogens into the surrounding soft tissues or possible recolonization of periodontal pockets from other diseased sites or intraoral niches.⁸ Power-driven instruments (i.e. sonic and ultrasonic scalers) have been introduced to further enhance the effectiveness of scaling and root planing (SRP). However, findings from clinical studies have also shown comparative outcomes following power-driven and manual instrumentation.⁹

Thus, the current evidence indicates that nonsurgical periodontal treatment may result in substantial clinical improvements in the great majority of cases, but none of the currently available instrumentation techniques are able to completely eliminate subgingival bacteria and calculus.⁷

Photodynamic therapy (PDT), also called photoradiation therapy, phototherapy, photochemotherapy, photo-activated disinfection (PAD), or light-activated disinfection (LAD), was introduced in medical therapy in 1904 as the light-induced inactivation of

cells, microorganisms or molecules and involves the combination of visible light, usually through the use of a diode laser and a photosensitizer.¹⁰

The photosensitizer is a substance that is capable to absorb light of a specific wavelength and transform it into useful energy. Each factor is harmless by itself, but when combined they can produce lethal cytotoxic agents that can selectively destroy cells.¹¹

Thus, PDT has been proposed as a modality to reduce bacterial load or even to eliminate periodontal pathogens.^{12, 13} The action mechanism of PDT has been extensively described previously.¹⁴ Briefly, upon illumination the photosensitizer is excited from the ground state to the triplet state. The longer lifetime of the triplet state enables the interaction of the excited photosensitizer with the surrounding molecules. It is anticipated that the generation of the cytotoxic species produced during PDT occurs while in this state.^{15, 16} The cytotoxic product, usually singlet oxygen ($^1\text{O}_2$), cannot migrate at a distance more than 0.02 μm after its formation, thus making it ideal for local application of PDT, without endangering distant molecules, cells or organs.¹⁶

In vitro studies have revealed that light from a Helium/Neon (He/Ne) laser or a Gallium-Aluminum-Arsenide (GaAlAs) laser, in combination with appropriate photosensitizers, can achieve a significant reduction in the viability of both aerobic and anaerobic bacteria in a solution of subgingival plaque from patients with chronic periodontitis.^{17, 18} Dobson & Wilson (1992) have shown that bacteria associated with periodontal disease can be killed through photosensitization with Toluidine Blue – O (TBO) and irradiation with a He/Ne soft laser.¹⁹ Subsequent studies in animals have shown PDT was distinctly advantageous in reducing the periodontal signs of redness and bleeding on probing, and significantly suppressed *P. gingivalis*.²⁰

During the last decade, a considerable interest has evolved in evaluating the use of PDT in the treatment of periodontal and peri-implant infections. However, despite the relatively abundant literature, the data on the clinical relevance of PDT when used in conjunction with mechanical therapy are still controversial and difficult to interpret for the clinician.

Therefore, the aims of this review article are: a) to provide an overview of the current evidence from randomized controlled clinical studies (RCTs) evaluating the potential clinical benefit for the additional use of PDT to mechanical debridement alone in nonsurgical periodontal therapy and b) to provide clinical recommendations for the use of PDT in periodontal practice.

Use of PDT as adjunct to nonsurgical periodontal therapy in patients with untreated chronic periodontitis (ChP)

A total of 18 RCTs have compared the potential additional benefit of PDT to SRP with the use of SRP alone in untreated periodontitis patients (Table 1). Eight out of the 18 studies have reported statistically significantly higher improvements in probing depth (PD) reduction and/or clinical attachment (CAL) gain following SRP + PDT compared to SRP alone,²¹⁻²⁸ [ENREF 22](#) while the rest of 10 studies have failed to reveal statistically significant differences in these parameters.^{29,30-38} An additional improvement for the reduction of bleeding on probing (BOP) following the use of PDT was reported in 5 out of the 19 papers.^{22, 26, 28, 31, 32} Changes of microbiological parameters were evaluated in 8 of 18 studies. Four studies have found a statistically significant effect of the additional use of PDT on the reduction of periodontal pathogens,^{28, 35, 37, 38} while 4 studies have failed to reveal any differences between the treatments groups.^{31, 33, 36, 39} Three out of the 18 studies have also evaluated the

changes in terms of various inflammatory markers.^{29, 33, 34} All three studies have revealed statistically significantly higher reductions in the investigated inflammatory markers following the additional use of PDT (Table 1).

Use of PDT as adjunct to nonsurgical periodontal therapy in patients with Aggressive Periodontitis (AgP)

Two RCTs have compared treatment with SRP + PDT to treatment with SRP alone,^{40, 41} and another study has compared SRP alone to PDT alone (i.e. without any mechanical debridement).^{42, 43} (Table 2). While one study has found in deep pockets (PD \geq 7 mm) statistically significant improvements in terms of PD reduction and CAL gain and significantly less periodontal pathogens of the red and orange complex and IL-1 β /IL-10 ratio following treatment with PDT,⁴¹ the other study has failed to reveal any statistical significant differences in the evaluated clinical and microbiological parameters between the treatments⁴⁰ (Table 2).

Use of PDT as adjunct to nonsurgical periodontal therapy in maintenance periodontitis patients

Eight RCTs have evaluated the potential additional benefit of PDT to SRP as compared with the use of SRP alone in maintenance patients (Table 3). Two out of the 8 studies have reported statistically significantly higher improvements in PD reduction and CAL gain following SRP + PDT compared to SRP alone.^{44, 45} An additional improvement for the reduction of BOP was reported in 5 out of the 8 studies.⁴⁴⁻⁴⁸

While three studies have found a statistically significant effect of the additional use of PDT on the reduction of periodontal pathogens,⁴⁶⁻⁴⁸ three other studies have failed to reveal statistically significant differences between the treatment groups.⁴⁹⁻⁵¹ Three out of the 8 studies have also evaluated the changes in terms of inflammatory markers.^{47, 50, 52} Two studies have revealed statistically significantly higher reductions in the investigated inflammatory markers following the use of PDT,^{47, 50} while one study detected no differences⁵² (Table 3).

Use of PDT as an alternative to systemic or local antibiotics

An extremely important aspect which needs to be kept in mind when considering the use of PDT, is the lack of bacterial resistance which gains even more importance in the light of the worldwide increase in bacterial resistance against antibiotics.⁵³ Thus, its repeated application in conjunction with mechanical debridement may represent a valuable future option for treating periodontal and peri-implant infections.^{11, 54} At present, there is however limited evidence on the possibility of PDT to replace systemic or local antibiotics.

A recent RCT study has evaluated the treatment of patients with AgP by means of nonsurgical periodontal therapy in conjunction with either systemic administration of amoxicillin and metronidazole or two-times topical application of PDT.^{55, 56} The results have shown that both treatment protocols resulted in statistically significant improvements in PD reduction, gain of CAL and improvement in BOP compared to baseline. The systemic use of amoxicillin and metronidazole yielded however, at both 3 and 6 months, statistically significantly higher reductions in mean PD compared with the treatment using PDT.^{55, 56} The most important clinical finding was the change in the total number of pockets ≥ 7 mm following both treatment protocols. In the PDT group, the total number of pockets ≥ 7 mm was reduced from 137 to 45 with the

corresponding values of 141 and 3 in the amoxicillin and metronidazole group. Moreover, compared to the results at 3 months, at 6 months, an additional decrease in the number of pockets ≥ 7 mm was measured.^{55, 56} On the other hand, the use of PDT has also led to statistically and clinically significant improvements compared to baseline, although the number of residual pockets needing further therapy was substantially higher compared with the use of systemic antibiotics (e.g. 45 vs. 3). The changes in clinical parameters were also accompanied by changes in the concentration of matrix metalloproteinases 8 and 9 (MMP-8 and -9) in the gingival crevicular fluid (GCF).⁵⁷ However, while in the antibiotic group, a statistically significant decrease of MMP-8 GCF level at both 3 and 6 months post treatment was observed, these changes were not significant in the PDT group.⁵⁷ Taken together, the available data suggest a rather limited clinical benefit of using PDT in the treatment of patients with AgP.^{40, 42, 43 56, 57} Thus, at the time being, PDT cannot be recommended as a replacement for systemic antibiotics in patients with AgP. On the other hand, no studies have compared the use of PDT or systemic antibiotics in conjunction with nonsurgical treatment in patients with ChP. Therefore, at present no conclusions can be made regarding this aspect.

The use of PDT as a potential alternative to local antibiotics has been recently evaluated in a RCT study comparing nonsurgical treatment of incipient peri-implantitis (sites with PD 4-6 mm, BOP positive and radiographic bone loss ≥ 2 mm) by means of mechanical debridement followed by either use of local antibiotics (e.g. minocycline) or application of PDT. The results at six months and at one year have failed to reveal statistically or clinically significant differences between the two treatment protocols, thus suggesting that PDT may represent a valuable alternative to local antibiotics during nonsurgical treatment of incipient peri-implantitis.^{58, 59}

Conclusions

Based on the available evidence from RCTs the following conclusions can be drawn:

- In patients with ChP the combination of SRP and PDT may result in substantially higher short-term clinical improvements evidenced by probing depth (PD) and/or bleeding on probing (BOP) reductions compared to SRP alone.
- In patients with aggressive periodontitis (AgP) the use of PDT cannot replace the systemic administration of amoxicillin and metronidazole. Due to lack of data, no conclusions can be made to what extent PDT may replace the use of systemic antibiotics in patients with ChP.
- Limited evidence from one study indicates that PDT may represent a possible alternative to local antibiotics in patients with incipient peri-implantitis.

Clinical recommendations

1. In patients with ChP, clinicians may consider the use of PDT in conjunction with subgingival mechanical debridement. However, due to limitations in time and costs, the use of PDT appears to be more suitable in the maintenance phase of therapy.
2. At present, the use of PDT cannot be recommended as an alternative to systemic antibiotics in the treatment of AgP or severe cases of ChP.

Figures 1 and 2: Clinical applications of PDT

Figure 1. Application of the phenothiazine chloride dye following subgingival SRP



Figure 2. Application of the low level laser light into the pocket



Tables 1, 2 and 3: Randomized clinical controlled studies, with SRP as control group

Table 1. Photodynamic therapy as initial periodontal therapy in patients with ChP (data of 18 studies reported in 19 publications)

Study Author Year Country Type	Diagnosis	Patients Female/male Age Smokers	Study duration	Treatment	Photosensitizer Laser	Laser parameters	Microbiology	Immunology	PD reduction (mm) CAL gain (mm) BOP reduction (%)
Al-Zahrani & Austah (2011) ²¹ Saudi-Arabia Split-mouth, RCT	ChP	n=17 0/17 41.6 ± 9.6 17 smokers	3 months	Test: SRP + PDT (1x) Control: SRP	Methylene blue (Ondine's Periowave, Ondine Biopharma, Vancouver, BC) Diode laser	Wavelength 670 nm	Not analysed	Not analysed	Test: PD: from 5.60±0.83 to 3.84±0.85 * CAL: from 6.30±1.44 to 4.70±1.27 * BOP: from 74.50±21.50 to 41.90±22.30 (n.s.) Control: PD: from 5.35±0.46 3.90±0.75 CAL: from 6.18±1.44 to 4.80±1.45 BOP: from 68.00±23.00 to 45.60 to 19.50.
Alwaeli et al. (2015) ²² Jordan Split-mouth, RCT	ChP	N=16 11/5 40.9±13.34	12 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride Diode Lases (HELBO, Photodynamic Systems, Grieskirchen, Austria)	Wavelength 660 nm, Output power 100mW Application time: 10s/site, 6 sites/tooth	Not analysed	Not analysed	Test: PD: 1.51±1.54* CAL: 1.48±1.89* BOP: 25%* Control: PD: 0.66±1.66 CAL: 0.13±1.7 BOP: 54%
Andersen et al. (2007) ²³ England Parallel, RCT	ChP	N=33 22/11 53 (18-75) unclear	12 weeks	Test 1: PDT Test 2: SRP+ PDT Control: SRP	Methylene blue (Periowave) Diode laser (Periowave)	Wavelength 670 nm Energy density 10-20 J/cm ² Max. power 150 mW Application time 60s/site	Not analysed	Not analysed	Test 1: PD: 0.67±0.44 (n.r.) CAL: 0.14±0.65 (n.r.) BOP: 73% (n.r.) Test 2: PD: 1.11±0.53* CAL: 0.86±0.61* BOP: 59% (n.s.) Control: PD: 0.74±0.43

Balata et al. (2013) ³⁰ Brazil Split-mouth, RCT	ChP	N=22 43.18 (31-62)	6 months	Test: SRP (ultrasonic)+P DT Control: SRP (ultrasonic)	Methylene blue 0.005% Low power laser (AsGaAl, Photon Laselll, Sao Paolo, Brazil)	Wavelength 660nm Output power 100mW Energy density 320 J/cm ² Dose 9 J Diameter tip 600 µm Application time: 90s/site	Not analysed	Not analysed	CAL: 0.36±0.35 BOP: 56% Test: PD decrease from 5.11±0.56 to 2.83±0.47 (n.s.) CAL change from 5.49±0.76 to 3.41 ± 0.84 (n.s.) BOP: from 61.58± 15.64 to 36.73±19.72 (n.s.) Control: PD decrease from 5.15±0.46 to 2.83±0.40 CAL change from 5.53±0.54 to 3.39 ± 0.51 BOP: from 62.23± 16.91 to 38.49±20.52
Berakdar et al. (2012) ²⁴ Germany Split-mouth, RCT	ChP	N=22 10/12 59.3±11.7 no smokers	6 months	Test: SRP+PDT Control: SRP	Methylene blue 0.005% Diode laser (Periowave)	Wavelength 670 nm Max. power 150 mW Application time 60s	Not analysed	Not analysed	Test: PD: 2.9±0.8* CAL: n.s. changes n.r. BOP: from 100% to 13.6% n.s. Control: PD: 2.4±0.8 BOP: from 100% to 22.7% CAL gain: n.s.
Betsy et al. (2014) ²⁵ India Parallel, RCT	ChP	N=88 51/39 39.6±8.7	6 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride trihydrate (freshly prepared, Sigma-Aldrich, USA) Diode laser (CNI Opto-electronics Tech., China)	Wavelength 655 nm, output power 1W Power density 60 mW/cm ² Diameter tip 0.5 mm Application time 60s/site	Not analysed	Not analysed	Test: PD: from 5.7 (5.0-6.0, 1.0) to 3.0 (2.0-6.0, 1.0)* CAL: from 6.5 (5.0-8.0, 1.4) to 4.0 (2.6-7.0, 2.0)* BOP: data n.r. Control: PD: from 5.5 (4.2-6.0, 1.0) to 4.0 (2.0-6.0, 1.0) CAL: from 6.0 (4.2-8.0, 1.7) to 4.5 (2.0-7.0, 2.0) BOP: data n.r.
Braun et al. (2008) ²⁶	ChP	N=20 11/9	3 months	Test: SRP +PDT	Phenothiazine chloride	Wavelength 660 nm	Not analysed	Not analysed	Test: Median (inter-quartile

Germany Split-mouth		46.6±6.1 no smokers		Control: SRP	(HELBO Photodynamic Sys., Austria)	Power output 100 mW Application time 10s/site			range, Max, Min) PD: 3.6 (0.6, 5.3, 3.2)* CAL: 7.04 (1.63, 9.11, 5.33)* BOP: 19 (11, 64, 2)* Control: Median (inter-quartile range, Max, Min) PD: 3.7 (0.6, 6.0, 3.4) CAL: 7.25 (2.02, 10.09, 5.61) BOP: 24 (21, 61, 2)
Christodoulides et al. (2008) ³¹ Parallel, RCT	ChP	N=24 13/11 45±8.11 3 smokers	6 months	Test: SRP + PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensiti- zer) Diode laser (HELBO TheraLite Laser)	Wavelength 670 nm Output power 75 mW Application time 60 s/tooth	No significant differences between the groups for <i>Aa</i> , <i>Pg</i> , <i>Tf</i> , <i>Td</i> , <i>Pi</i> , <i>Pm</i> , <i>Fn</i> , <i>Cr</i> , <i>En</i> , <i>Ec</i> , <i>Cs</i>	Not analysed	Test: PD: 0.9±0.3 (n.s.) CAL: 0.7±0.3 (n.s.) BOP: from 54±16% to 10±5%* Control: PD: 0.7±0.7 CAL: 0.5±0.5 BOP: from 59±21% to 20±4%
Dilsiz et al. (2013) ²⁷ Turkey Split-mouth, RCT	ChP	N=24 14/10 40.7±7.3 no smokers	6 months	Test1: PDT + SRP Test2: KTPL + SRP Control: SRP	Methylene blue 1% Diode Laser (Doctor Smile diode, Lambda Scientifica Vincenza , Italy)	Wavelength 808 nm Output power 100 mW Application time 60 s/site Dose 6J Fibre tip diameter 300 µm	Not analysed	Not analysed	Test 1: PD: 1.54±0.59* CAL: 1.54±1.10* BOP: from 88±0.34 to 38±0.49 (n.s.) Test 2: PD: 2.08±1.02* CAL: 2.42±1.14* BOP: from 96±0.20 to 42±0.50 (n.s.) Control: PD: 1.42±0.88 CAL: 1.50±0.88 BOP: from 92±0.28 to 46±0.51
Ge et al. (2011) ³² China Parallel, RCT	ChP	N=58 28/30 43±10 9 smokers	12 weeks	Test 1: SRP + PDT (once) Test 2: SRP + PDT (twice)	Methylene blue 0.01% Diode Laser (Periowave)	Wavelength 670 nm Output power 140 mW Energy density 21 J/cm ²	Not analysed	Not analysed	No significant difference for PD reduction and CAL gain. Significant higher BOP reduction in both test groups compared to the

				Control: SRP		Application time 60 s/site Dose 6 J			control group.
Luchesi et al. (2013) ³³ Brazil Parallel, RCT	ChP Furcation defects	N=37 no smokers	6 months	Test: SRP+PDT Control: SRP+non activated laser	Methylene Blue Diode laser (Thera Lase DMC, Sao Paulo, Brazil)	Wavelength 660 nm, power output 60 mW Energy dose 129 J/cm ² Fibre optics diameter 600 µm Application time 60s/site	Significant decrease in <i>P.g.</i> and <i>T.f.</i> in PDT group, however no significant differences between the groups.	Significant reduction at 3 months of GM-CSF, IFN- γ, IL-6, and IL-8 in favour to PDT. At 6 m, also significant reduction of IL-1β in PDT group.	No significant differences between the groups. Test: PD: 1.59±1.11 (n.s.) CAL: 0.78±1.54 (n.s.) BOP: from 100% to 37.50% (n.s.) Control: PD: 1.50±1.73 CAL: 1.00±1.69 BOP: from 100% to 55%
Lui et al. (2011) ³⁴ China Split-mouth, RCT	ChP	N=24 14/10 50 no smokers	3 months	Test: SRP+PDT Control: SRP	Methylene blue Diode laser (Ezlase, BIOLASE Techn., USA)	Wavelength 940 nm Energy 1 W Application time 30 s/tooth Energy density 4 J/cm ² Fibre tip diameter 300 µm	Not analysed	Significant reduction of IL-1β at 1 wk in favour to PDT. Significant reduction of GCF at 1wk and 1 m in favour to PDT.	Changes from baseline to 3 m: Test: PD: from 4.7±0.8 to 3.1±0.4 (n.s.) REC: from 0.8±1.2 to 1.8±1.2 (n.s.) BOP from 94±06 to 39±14 (n.s.) Control: PD from 4.5±0.7 to 3.2 ± 0.3 REC from 1.0±1.1 to 1.8±1.3 BOP from 92±10 to 43±12
Mettraux & Hüsler (2011) ³⁵ Switzerland Split-mouth, RCT	ChP	N=19	6 months	Test: SRP+PDT Control: SRP	Methylene Blue Softlaser (Lasotronic MED-701, Orcos Medical, Switzerland)	Wavelength 670nm, Energy output 330 mW Energy density 31 J/cm ² Application: transgingival 1min/site Fiber tip diameter 8mm	Significant reduction of the total bacterial load in favour to PDT. Significant reduction of <i>T.d.</i> in both groups.	Not analysed	Test: PD: 2.1±1.4 (n.s.) CAL: 1.5±1.3 (n.s.) Control: PD: 1.5±1.6 CAL: 0.9±1.7
Polansky et al.	ChP	N=58	3	Test: SRP +	Phenothiazine	Wavelength	No significant	Not analysed	Test:

(2009) ³⁶ Austria Parallel, RCT		36/22 48.7 (25-67) 7 smokers	months	PDT Control: SRP (ultrasound)	chloride (HELBO Blue Photosensitizer) Diode laser (HELBO Minilaser 2075 F, Grieskirchen, Austria)	680 nm Output power 75 mW Application time 60 s/site	difference for the reduction of <i>P.g.</i> between the groups; significant reduction of <i>P.g.</i> at 3 months compared to baseline in both groups.		PD: from 5.79±1 to 4.55±1.14 (n.s.) CAL: from 6.60±1.37 to 5.25±1.41 (n.s.) BOP: from 100 to 47% (n.s.) Control: PD: from 5.53±1.15 to 4.50±1.33 CAL: from 6.59±1.23 to 5.24±1.48 BOP: from 100% to 59%
Queiroz et al. (2014) ³⁹ Brasil Split-mouth, RCT	ChP	N=20 11/9 46.05±6.38 (35-55) smokers only	3 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO Minilaser 2075 F, Grieskirchen, Austria)	Wavelength 660 nm, Maximum power 60mW/ cm ² Fiber tip diameter 0.6 mm Application time 10 s/site at 6 sites/tooth	40 subgingival bacteria were analysed: no significant differences between the groups or the timepoints	Presented in Queiroz et al 2015 ²⁹	Presented in Queiroz et al. 2015 ²⁹
Queiroz et al. (2015) ²⁹ Brasil Split-mouth, RCT	ChP	N=20 11/9 46.05±6.38 (35-55) smokers only	3 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO Minilaser 2075 F, Grieskirchen, Austria)	Wavelength 660 nm, Maximum power 60mW/ cm ² Fiber tip diameter 0.6 mm Application time 10 s/site at 6 sites/tooth	Presented in Queiroz et al. 2014 ³⁹	Significant reduction of IL- 1β at 1 wk in favour to PDT. Significant reduction of MMP 8 at 12 wk in favour to PDT.	No significant differences between the groups. Test: PD: 1.58±1.28 (n.s.) CAL: 1.41±1.58 (n.s.) Control: PD: 1.81±0.52 CAL: 1.60±0.92
Sigusch et al. (2010) ²⁸ Parallel, RCT	ChP	N=24 17/7 32-58 no smokers	12 weeks	Test: SRP + PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO Thera Lite Laser)	Wavelength 660 nm Power density 60 mW/cm ² Application time 10 s/site	Significant reduction of <i>F.n.</i> in the test group compared to the control group.	Not analysed	Test: Significant difference at 12 weeks between the groups regarding mean PD* (data n.r.) Median, interquartile range: CAL: 2.45, 0.68*

Srikanth et al. (2015) ³⁷ India Split-mouth, RCT	ChP	N=39 (30-55) nonsmokers	6 months	Test1: SRP+PDT Test 2: SRP +laser without photosensitizer Control: SRP	Indocyanine green (Aurolabs) Diode laser (firm not specified)	Wavelength 810 nm Power output 0.7 W Application time 5 s/site	Significant decrease of the % of viable bacteria in favour to PDT	Not analysed	REC: 0.20, 0.18 BOP: from 66 to 18 %* Control: Median, interquartile range: PD: data n.r. CAL: 0.20, 0.18 REC: 0.20, 0.10 BOP: from 68 to 72% Test 1: PD: from 5.81±0.89 to 3.07±0.68(n.s.) CAL: from 5.00±0.80 to 2.53±0.58 (n.s.) BOP: n.r. Test 2: PD: 5.34±0.34 to 3.15 v 0.43 (n.s.) CAL: from 4.57±0.57 to 2.96±0.44* BOP: n.r. Control: PD: from 5.07±0.27 to 3.01±0.21 CAL: from 4.50±0.50 to 3.10±0.01 BOP: n.r.
Theodoro et al. (2012) ³⁸ Brazil Split-mouth, RCT	ChP	N=33 21/12 43.12±8.2 nonsmokers	6 months	Test1: SRP + PDT Test2: SRP + Placebo PDT Control: SRP	Phenothiazine 100 µg/ml (Sigma Chemical, St. Louis, USA) Diode Laser (BioWave)	Wavelength 660 nm Power output 30 mW Power intensity 0.4 W/cm ² Energy density 64.28 J /cm ² Application time 150 s/site Spot size 0.07 cm ²	<i>A.a., P.g., P.i., T.f., P.n.</i> Significant differences in all investigated periodontopathog ens in favour to SRP + PDT.	Not analysed	Test 1: PD: from 5.75± 1.44 to 3.42±1.15 (n.s.) CAL: from 6.52±2.11 to 4.96±2.07 (n.s.) BOP: from 93.9% to 45.5% (n.s.) Test 2: PD: from 5.88±1.26 to 2.48±1.0 (n.s.) CAL: from 6.37±1.56 to 4.38±1.82 (n.s.) BOP: from 97% to 39.4% (n.s.) Control: PD: from 5.81±1.0 to

3.1±0.83
CAL: from 6.23±1.25 to
4.25±1.73
BOP: from 97% to 27.3%

n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; MMP: Matrixmetalloproteinases; *T.f.*: *Tannerella forsythia*, *P.g.*: *Porphyromonas gingivalis*; *A.a.*: *Aggregatibacter actinomycetemcomitans*; *T.d.*: *Treponema denticola*; *F.n.*: *Fusobacterium nucleatum*; *P.i.*: *Prevotella intermedia*; *C.r.*: *Campylobacter rectus*; *E.c.*: *Eikenella corrodens*; *P.m.*: *Parvimonas micra*; *E.n.*: *Eubacterium nodatum*; *C.s.*: *Capnocytophaga Spp.*

Table 2. Photodynamic therapy as initial periodontal therapy in patients with AgP (data of 3 studies reported in 4 publications)

Study Author Year Country Type	Diagnosis	Patients Female/male Age Smokers	Study duration	Treatment	Photosensitizer Laser	Laser parameters	Microbiology	Immunology	PD reduction (mm) CAL gain (mm) BOP reduction (%)
Chitsazi et al. (2014) ⁴⁰ Iran Split-mouth, RCT	AgP	N=24 15/9 29	3 months	Test: SRP+PDT Control: SRP	Toluidine Blue photosensitizer (Sigma chemical Co., St. Louis, Mo) Diode Laser (HANDY Laser, USA)	Wavelength 670-690 nm Power 75 mW Application time 2 min/site	No significant differences for the levels of A.a. were observed between the groups	Not analysed	Test: PD change: from 5.79±1.06 to 4.29±0.95 (n.s.) CAL change: from 6.58±0.83 to 5.29±1.26 (n.s.) BOP change: from 91.7% to 75% (n.s.) Control: PD change: from 5.45±0.71 to 4.54±0.88 CAL change: from 6.25±1.07 to 5.50±1.18 BOP change: from 100% to 37.5%
Moreira et al. (2015) ⁴¹ Brazil Split-mouth, RCT	AgP	N=20 30.6±4.25 18/2 non smokers	3 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photodynamic systems, Grieskirchen, Austria) Diode laser (HELBO Minilaser 2075 F, Grieskirchen, Austria)	Wavelength 670 nm Maximum power 75 mW Fiber tip diameter 0.6 Mm Energy density 2.49 J/ cm ² Application time 10s/site	Significant less periodontal pathogens of the red and orange complex in the test group.	Significant less IL-1β/IL-10 ratio in the test group.	No differences between the groups for moderate pockets. In deep pockets (PD≥7mm), significant PD decrease and CAL gain in favour to PDT: Test (deep pockets): PD from 7.73±0.87 to 3.77±0.97 * CAL: from 7.84±0.89 to 5.07±0.64* BOP: from 144±60 to 22±13.75 (n.s.) Control (deep pockets): PD: from 7.68±0.92 to 5.12±0.8 CAL: from 7.75±1.21 to 6.00±1.04. BOP: from 154±64.16 to 36±15

Novaes et al. (2012) ⁴³ Brazil Split-mouth, RCT	AgP	N=10 8/2 31 (18-35) nonsmokers	3 months	Test: PDT Control: SRP	Phenothiazine chloride (Helbo blue photosensitize r) Minilaser (HELBO, Grieskirchen, Austria)	Wavelength 660 nm, Power 0.06W/ cm ² , fluency 212.23 J/ cm ² Application time 10s/site	40 subgingival species were determined. PDT reduced significantly <i>A.a.</i> compared to SRP; SRP is more efficient for the red complex than PDT. In PDT a recolonisation of <i>T.f.</i> and <i>P.g.</i> was observed.	Not analysed	Published in Oliveira et al. 2007 ⁴²
Oliveira et al. (2007) ⁴² Brazil Split-mouth, RCT	AgP	N=10 8/2 31 (18-35) nonsmokers	3 months	Test: PDT Control: SRP	Phenothiazine chloride (Helbo blue photosensitize r) Minilaser (HELBO, Grieskirchen, Austria)	Wavelength 660 nm, Power 60 mW/ cm ² , fluency 212.23 J/ cm ² Application time 10s/site	Published in Novaes et al. 2011	Not analysed	Test: PD: from 4.92±1.61 to 3.49±0.98 (n.s.) CAL: from 9.93±2.10 to 8.74±2.12 (n.s.) BOP: from 57% to 19% (n.s.) Control: PD: from 4.92±1.14 to 3.98±1.76 CAL: from 10.53±2.30 to 9.01±3.05 BOP: from 60% to 21%

n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; *T.f.*: *Tannerella forsythia*, *P.g.*: *Porphyromonas gingivalis*; *A.a.*: *Aggregatibacter actinomycetemcomitans*; *T.d.*: *Treponema denticola*; *F.n.*: *Fusobacterium nucleatum*; *P.i.*: *Prevotella intermedia*; *C.r.*: *Campylobacter rectus*; *E.c.*: *Eikenella corrodens*; *P.m.*: *Parvimonas micra*; *E.n.*: *Eubacterium nodatum*; *C.s.*: *Capnocytophaga* Spp.

Table 3. Photodynamic therapy in Supportive Periodontal Therapy (data of 8 studies reported in 9 publications)

Study Author Year Country Type	Diagnosis	Patients Female/male Age Smokers	Study duration	Treatment	Photosensitizer Laser	Laser parameters	Microbiology	Immunology	PD reduction (mm) CAL gain (mm) BOP reduction (%)
Campos et al. (2013) ⁴⁴ Brazil Split-mouth, RCT	ChP	n=13 8/5 48.15±7.53 no smokers	3 months	Test: SRP+PDT Control: SRP	Methylene blue 10 mg/ml Diode laser (Thera Lase- DMC, Brazil)	Wavelength 660 nm Power output 60 mW Energy density 129 J/cm ² Application time 60s/site	Not analysed	Not analysed	Test: PD: 2.17±0.91* CAL: 1.43±1.61* BOP: 77.78* Control: PD: 1.14±1.53 CAL: 0.51±0.76* BOP: 40%
Cappuyens et al. (2012) ⁴⁹ Switzerland Split-mouth, RCT	ChP	N=29 8/21 52 (36-74) 12 smokers	6 months	Test 1: SRP+PDT Test 2: SRP+Diode Soft Laser (DSL) Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitize r) Diode Laser (Helbo Photodynamic Sys)	Wavelength 660 nm Power output 40 mW Application time 60s/site	<i>A.a., P.g., T.f., T.d., total bacterial load</i> No significant difference in the investigated microbiological parameters. However, <i>P.g., T.f., and T.d.</i> were suppressed stronger in the PDT group.	Not analysed	Test 1: PD: from 5.6±1.2 to 3.8±1.2 (n.s.) REC: from 0.8±1.3 to 1.0±1.3 (n.s.) BOP: at 6m 15% (n.s.) Test 2: PD: from 5.5±0.7 to 3.9±1.0 (n.s.) REC: from 0.8±1.7 to 1.3±1.8 (n.s.) BOP: at 6m 18% (n.s.) Control: PD: from 5.5±1.0 to 3.6±1.1 REC: from 0.7±1.3 to 1.0±1.3 BOP: at 6m 12%
Chondros et al. (2009) ⁴⁶ Netherlands Parallel, RCT	ChP	N=24 14/10 Test: 50.6±9.2 Control: 48.3±7.9 7 smokers	6 months	Test: SRP+PDT Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitize r) Diode laser (HELBO minilaser 2075F)	Wavelength 670 nm Output power 75 mW/cm ² Application time 60 s/tooth	<i>A.a., P.g., P.i., T.f., T.d., P.m., F.n., C.r., E.n., E.c., C.s.</i> Significant reduction of <i>T.d., E.c., C.s.</i> was found in favour of SRP+PDT	Not analysed	Test: PD: 0.8±0.5 (n.s.) CAL: 0.7±0.7 (n.s.) BOP: from 15±12 to 12±05* Control: PD: 0.9±0.8 CAL: 0.5±0.6 BOP: from 19±14 to 18±08

Giannopoulou et al. (2012) ⁵² Switzerland Split-mouth, RCT	ChP	N=29 8/21 52 (36-74) 12 smokers	6 months	Test 1: SRP+PDT Test 2: SRP+diode laser (DL) Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode Laser (Helbo Photodynamic Sys, Grieskirchen, Austria)	Wavelength 660 nm Power output 100 mW Application time 60s/site	Analysed in Cappuyns et al. 2012	Levels of 13 cytokines and 9 acute-phase proteins were measured. No significant differences were observed between the groups at any time point.	See Cappuyns et al. 2012
Kolbe et al. (2014) ⁴⁷ Brazil Split-mouth, RCT	ChP	N=21 12/10 48.52 (32-75) non smokers	6 months	Test 1: PDT Test 2: Photosensi tizer Control: SRP	Methylene blue (10 mg/ml) Diode laser (Thera Lase, Brazil)	Wavelength 660 nm Power output 60 mW Energy dose 129 J/cm ² Application time 60s/site	Lower * levels of A.a. were detected in Test1 and Control groups at 3 as compared to 6 months. Lower * detection frequency of <i>P.g.</i> for Test 1 and Control groups.	IL-4 increased *in Test 1. IL-10 was reduced *in Test 2. Test 1 showed significant reduction of IL- 6, IL-1 β IFN- γ .	Test 1: PD: 1.6 \pm 1.20 (n.s.) CAL: 0.95 \pm 1.38 (n.s.) BOP: from 100% to 28.57% (n.s.) Test 2: PD: 1.29 \pm 1.22 (n.s.) CAL: 0.69 \pm 1.30 (n.s.) BOP: from 100% to 61.90%* Control: PD: 1.88 \pm 0.97 CAL: 1.21 \pm 0.96 BOP: from 100% to 28.57%
Lulic et al. (2009) ⁴⁵ Parallel RCT	ChP	N=10 3/7 54 (40-74) 2 smokers	12 months	Test: SRP + PDT Control: SRP+ Placebo: PDT	Phenothiazine chloride (HELBO Blue Photosensitizer) Diode laser (HELBO Minilaser 2075 F)	Wavelength 670 nm Output power density 75 mW/cm ² Application time 60 s/site	Not analysed	Not analysed	Test: PD: -0.27 \pm 0.43* CAL: -0.09 \pm 0.41* BOP decrease 97-77* Control: PD: -0.07 \pm 0.61 CAL: -0.20 \pm 0.61 BOP increase 84-87
Müller Campanile et al. (2015) ⁵⁰ Switzerland Split-mouth, RCT	ChP	N=27 13/14 62.8 (37-77)	6 months	Test1: SRP + PDT (twice) Test2: SRP + PDT (once) Control: SRP+	Methylene blue Diode laser (Periowave, Ondine Biomedical, Vancouver, Canada)	Wavelength 670 nm Power output 280 mW Application time 60 s/site	No significant changes of the microorganisms from baseline to 3 / 6 months in any of the group.	No significant differences between the groups for IL- 1 β , IL-1ra, IL- 8, IL-17, b- FGF, G-GSF, GM-CSF, IFN-	Test 1: PD: from 5.9 \pm 0.9 to 3.1 \pm 1.0 (n.s.) CAL: from 7 \pm 1.6 to 4.1 \pm 1.6 (n.s.) BOP: from 16 to 10 sites (n.s.) Test 2:

				inactivated laser				γ, MIP-1β, VEGF, TNF-α. C-reactive protein was significantly lower in the Test1 group, compared to the others.	PD: from 6.3± 1.3 to 2.9±1.8 (n.s.) CAL: from 7.9± 2.2 to 4.2±2.8 (n.s.) BOP: from 20 to 7 sites (n.s.) Control: PD: from 6.3± 1.5 to 3.4±1.5 CAL: from 7.6± 2 to 4.6±2.2 BOP: from 15 to 10 sites
Petelin et al. (2014) ⁴⁸ Slovenia Parallel, RCT	ChP	N=27 12/15 nonsmokers	12 months	Test 1: ultrasonic scaling (US)+PDT Test 2: US Control: SRP	Phenothiazine chloride (HELBO Blue Photosensitize r) Diode laser (HELBO Tera Light)	Wavelength 660 nm Output power density 60 mW/cm ² Application time 60 s/site	Assessment of <i>A.a.</i> , <i>P.g.</i> , <i>P.i.</i> , <i>T.f.</i> , <i>T.d.</i> Significant reduction of <i>T.d.</i> + sites and of <i>A.a.</i> , <i>T.f.</i> , <i>T.d.</i> levels in favour to PDT in medium pockets (4-6mm), and of <i>T.d.</i> in deep pockets (>6mm).	Not analysed	Test 1: PD from 3.4±0.2 to 2.9±0.2 (n.s.) CAL from 4.2±0.3 to 3.7±0.2 (n.s.) BOP from 25% to 9 %* Test 2: PD from 3.6±0.2 to 3.0±0.2 (n.s.) CAL from 4.3±0.3 to 3.7±0.2 (n.s.) BOP from 23% to 12% (n.s.) Control: PD from 3.8±0.2 to 3.3±0.2 CAL from 4.7±0.3 to 4.0±0.2 BOP from 17% to 9% No significant differences between the groups: Test: PD: from 3.5±0.4 to 3.3±0.4 (n.s.) CAL: from 11.4±1.7 to 11.4±1.6(n.s.) BOP: from 5.4±4.6 to 3.3±4.3 (n.s.) Control: PD: from 3.3±0.5 to 3.1±0.4 CAL: from 10.6±1.3 to
Rühling et al. (2010) ⁵¹ Germany Parallel, RCT	ChP	N=60 48±8 nonsmokers	3 months	Test: PDT Control: Ultrasonic debridement	5% tolonium chloride (Asklepion Meditec, Fife, UK) Diode laser (SaveDent Dental Laser Sydstem, Asclepion Meditec. Ltd., Fife, UK)	Wavelength 635 nm Energy dose 100 mW Application tie 60 s/site	Assessment of Microbial counts were reduced after treatment but returned to baseline values after 3 months.	Not analysed	

10.7±1.2
BOP: from 4.7±4.8 to
5.7±8.7

n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; b-FGF: basic fibroblast growth factor; G-CSF: granulocyte colony stimulating factor; IFN- γ : interferon γ ; MIP-1 β : macrophage inflammatory protein 1 β ; GM-CSF: granulocyte macrophage colony stimulating factor; TNF- α : tumor necrosis factor α ; CRP: C-reactive protein; VEGF: vascular endothelial growth factor; *T.f.*: *Tannerella forsythia*, *P.g.*: *Porphyromonas gingivalis*; *A.a.*: *Aggregatibacter actinomycetemcomitans*; *T.d.*: *Treponema denticola*; *F.n.*: *Fusobacterium nucleatum*; *P.i.*: *Prevotella intermedia*; *C.r.*: *Campylobacter rectus*; *E.c.*: *Eikenella corrodens*; *P.m.*: *Parvimonas micra*; *E.n.*: *Eubacterium nodatum*; *C.s.*: *Capnocytophaga Spp.*

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